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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/608,865	06/27/2003	David Lewin	09800080-0131	8197

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EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 04/06/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/608,865	LEWIN ET AL.	
	Examiner	Art Unit	
	Daniel M. Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 June 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/1/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This is the First Office Action on the Merits of the application filed 27 June 2003 as a continuation of 09/691,439, which claims benefit of US provisional application 60/160,246 filed 19 October 1999. The preliminary amendments filed 27 June 2003 and 25 January 2006 have been entered. Claims 1-51 were originally filed. Claims 17-50 were cancelled in the 27 June amendment. Claims 9-16 were amended and claim 51 was canceled in the 25 January amendment. Claims 1-16 are pending.

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-16 wherein the expression detected is that of the OB1 gene, in the reply filed on 25 January 2006 is acknowledged. The traversal is on the ground(s) that it would not be unduly burdensome to search and examine all of the claims. This is not found persuasive because, as stated in the previous Office Action, each method is limited to analyzing the expression of a gene to which the other methods are not limited. Therefore, examination of each method requires a separate search for the gene that distinguishes the respective methods. In addition, because each method encompasses subject matter not encompassed by the other methods, a determination that any one method is patentable over the art does not adequately support patentability of any of the other methods. Therefore, patentability of each method must be determined separately.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-16 will be examined to the extent that they read on the claimed method wherein the expression detected is that of the OB1 gene. The methods wherein the OB1 gene is not

detected are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the 25 January reply.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention and Breadth of the claims: The claims are directed to a method of assessing the efficacy of an obesity treatment or identifying a therapeutic agent for treating

obesity in a subject comprising assessing the expression of one or more genes selected from the genes identified in the application as OB1-6. On page 26 of the specification, the application teaches, "The differentially expressed OB sequences identified herein...allow for the course of treatment of a pathophysiology to be monitored...If the reference cell population contains cells not exposed to the treatment and not suffering from the disorder, then a difference in expression between OB sequences in the test population and this reference cell population indicates the treatment is not efficacious. However, similarity in expression between OB sequences in the test cell population and the reference cell population described above indicates that the treatment is efficacious." Thus, the claimed invention, viewed in light of the specification, is directed to methods wherein expression of the OB genes is used as a surrogate endpoint for therapeutic efficacy in the treatment of obesity. It is further noted that the claims generally cover a methods of assessing therapeutic efficacy in treatment of obesity irrespective of etiology and wherein the test cell population can be any cell population "capable of expressing one or more nucleic acid sequences selected from the group consisting of OB 1-6".

State of the prior art and level of predictability in the art: The art provides no guidance specific to the use of the genes identified in the instant application as OB 1-6 as surrogate endpoints for obesity. The art does teach, however, that before a putative biomarker can be used as a surrogate endpoint it must be validated as such. Wagner (2002) *Dis. Markers* 18:41-46 acknowledges in the Abstract, "Putative biomarkers are typically identified because of a relationship to known or hypothetical steps in a pathophysilogic cascade. Biomarker discovery can also be effected by expression profiling experiment using a variety of array technologies and related methods." However, Wagner cautions, "A rational basis for recommending the use of a

putative biomarker does not guarantee the utility of the biomarker or its qualification as a surrogate endpoint" (paragraph bridging the left and right columns on page 43) and "Biomarkers require validation in most circumstances" (paragraph bridging pages 43-44).

Frank *et al.* (2003) *Nature Rev.* 2:566-580 concurs, stating, "The standard concepts of test-re-test reliability and validity apply with equal force to clinical biomarkers as they do in any assay system" and, "The work required to establish the reliability and validity of a new biomarker should not be underestimated in general, and in particular needs of planning for each combination of clinical indication and mechanism of action" (paragraph bridging the left and right columns on page 568). Feng *et al.* (2004) *Pharmacogenomics* 5:709-719 teaches, "The development and validation of clinically useful biomarkers from high-dimensional genomic and proteomic information pose great research challenges. Present bottle necks include: that few of the biomarkers showing promise in initial discovery were found to warrant subsequent validation...A molecular profiling approach, although promising, has a high chance of yielding biased results and overfitted models" (Abstract).

Viewed as a whole, the art clearly teaches that the utility of a putative biomarker as a surrogate endpoint for any disease state is unpredictable and must be validated.

With regard to using a gene identified in experiments with the ob/ob mouse (See Infra.) as a general marker for therapeutic outcome in the treatment of obesity in mammals or humans, the art evidences additional unpredictability.

The art teaches that the ob/ob mouse is not necessarily a model for obesity in general or for the effects of leptin in other mammals. Popovic *et al.* (2001) *Pituitary* 4:7-14 teaches, "Experiments in rodents have shown that leptin activates the sympathetic nervous system, is

involved in regulation of blood pressure, hematopoiesis, immune function, angiogenesis and brain, bone and pituitary development. Some biological effects expected based on observations in rodents, have so far not been seen in humans. Thus due to species differences in the role of leptin it is difficult to translated the data from rodents to human physiology" (Abstract; emphasis added). Jéquier *et al.* (2002) *Ann. N.Y. Acad. Sci.* 967:379-388 points out additional evidence of distinct roles for leptin in rodents and humans. For example, in the section entitled "Does leptin act as a satiation or a satiety signal?" bridging pages 382-383, Jéquier *et al.* concludes based on several lines of evidence that leptin acts as a satiety factor in mice but not in humans.

Likewise, Gorden *et al.* teaches that leptin accelerates the onset of puberty in normal mice (page 656, right column, first paragraph) but does not induce puberty in humans (page 656, right column, second paragraph). Gorden *et al.* teaches, "[Leptin] was discovered in a rodent model; these models have been important guides in further understanding leptin physiology. There might be differences among rodent models, however, as a result of the quantitative severity of the phenotype and genetic background. Therefore, rodent models might not predict the human physiological or pharmacological response to leptin administration" (second full paragraph in the right column on page 657; emphasis added).

The concern of Gorden *et al.* regarding differences among rodent models is echoed in the teachings of Takahashi *et al.* (2002) *Horm. Metab. Res.* 34:691-697, which teaches:

> We observed strain differences in responsiveness to reduced and elevated leptin levels. A reduction in leptin during fasting evoked a greater response in C57Bl/6J mice by decreasing energy expenditure and thyroxin, increasing corticosterone and stimulating food intake and weight gain during refeeding. However, C57Bl/6J mice were less responsive to an increase in leptin in the fed state. Conversely, the leptin-mediated response to fasting was blunted in SWR/J mice, whereas an increase in leptin profoundly reduced food intake and body weight in SWR/J mice fed *ad libitum*. Sensitivity to fasting in C57Bl/6J mice was associated with higher hypothalamic NPY mRNA and reduced POMC and UCP-

> 1 mRNA expression, while the robust response to high leptin levels in SWR/J mice was associated with suppression of NPY mRNA. These results indicate that differences in leptin responsiveness between strains might occur centrally or peripherally, leading to alteration in the patterns of food intake, thermogenesis and energy storage.

Viewed as a whole, these teachings clearly show that the physiological effects of leptin in a single strain of mouse cannot reliably extrapolated to all species of mammal, as variation is evident even among different strains of mouse.

It is further noted that the ob/ob mouse used in the experiments disclosed in the application, unlike the vast majority of obese humans, does not express endogenous leptin. Furthermore, Jéquier *et al.* teaches, "Similar to rodents with DIO [diet induced obesity], human obese subjects have high plasma leptin concentrations that do not induce the expected responses (*i.e.*, reduction in food intake and an increase in energy expenditure). This suggests that obese humans are resistant to the effects of endogenous leptin. Leptin resistance is also demonstrated in obese patients by the lack of effect of exogenous leptin administration to induce weight loss" (first full paragraph on page 384; emphasis added). This is in marked contrast to the response of the ob/ob mouse to administration of exogenous leptin, wherein administration leads to dramatic reduction in apatite and induces weight loss.

Still further, Naggert *et al.* US Patent No. 5,593,837 reports that, unlike the ob/ob mouse used in the instant working examples wherein expression of the OB1 gene (known in the art as PC2) was elevated relative to littermate controls, there was no change in the expression of PC2 in fat/fat obese mice relative to littermate controls (see especially column 2, lines 45-65).

Thus, the general applicability of OB1 expression as a marker for obesity and responsiveness to agents that affect obesity is clearly unpredictable.

Finally, with regard to the broad scope of the method practiced with any test cell population, Renz *et al.* (2000) *J. Biol. Chem.* 275:10429-10436, which is Applicant's own post-filing disclosure, teaches, "We do not yet know whether the effect of leptin on *PC2* expression is limited to particular cell types" (second paragraph on page 10433). Thus, it is clear that at the time of filing test cell populations that could be used in the claimed method, other than pituitary cells, remained to be identified.

Amount of direction provided by the inventor and existence of working examples: The instant application identifies the PC2 gene and other genes expressed in the pituitary gland as induced in ob/ob mice as compared to litter mate controls and suppressed in ob/ob mice in response to the administration of exogenous leptin (see especially Example 10, commencing on page 72, and Table 5, page 75). Based on this, the application generally asserts that expression of the identified genes can be used to assess the efficacy of an obesity treatment in a subject and to identify agents that modulate obesity (see especially page 26-27). However, the application provides no evidence to validate that expression of the OB1 gene is a useful biomarker or surrogate endpoint for obesity. In particular, no evidence is provided to indicate that expression of the OB1 gene (*i.e.*, PC2) is altered in any way in animals other than the ob/ob mouse either as a consequence of obesity or in response to an agent that might be useful in the treatment of obesity.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the relative level of skill in the art is high, the skilled artisan would not be able to use the claimed invention to assess the efficacy of an obesity treatment in a subject of identify a test therapeutic agent for treating obesity without first having to engage in undue

experimentation to establish that expression of the OB1 gene is a valid marker for obesity and response to anti-obesity therapeutics. The art clearly establishes that putative biomarkers must be validated and that "few of the biomarkers showing promise in initial discovery were found to warrant subsequent validation" (Feng *et al.*, *Id.*). Furthermore, the art teaches that physiological responses identified in the ob/ob mouse cannot be predictably extended to obesity in general and all species of mammal. Still further, according to Applicant's own post-filing disclosure, the practicability of the claimed invention with test cell populations other than pituitary cells remained unknown at the time of filing.

Given this high degree of unpredictability and the absence of any evidence to indicate that OB1 gene expression is a valid surrogate endpoint for obesity, the basic premise underlying the claimed invention is no more than a theoretical possibility. This is not sufficient to meet the enablement requirement of 35 USC §112, first paragraph.

> Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. *See Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that 'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.') Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. *Genentech Inc. v. Novo* Nordisk A/S (CA FC) 42 USPQ2d 1001, 1005.

In view of the foregoing, it would require undue experimentation to practice the invention claimed. Therefore, the claims are properly rejected under 35 USC §112, first paragraph, as lacking an enabling disclosure.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 6 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claim is indefinite in reciting, "comparing 6 or more of the nucleic acid sequences". As the base claim is limited to detecting expression of one or more sequences selected from OB1-6, it would appear that there is no antecedent for detection of more than 6 of the nucleic acid sequences.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 571-272-0779. The examiner can normally be reached on Monday through Friday 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

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